CANCER IN PREGNANCY: MATERNAL AND FETAL RISKS

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1

Cancer in pregnancy: identification of unanswered questions on maternal and fetal risks

G. KOREN, M. LISHNER AND D. ZEMLICKIS

When cancer occurs in pregnancy, there is almost always a conflict between optimal maternal therapy and fetal well-being. Consequently, either maternal or fetal health, or both, may be compromised.

Very sparse data exist on maternal outcome after cancer treatment in pregnancy. In addition, the literature on fetal outcome following maternal cancer is composed mainly of case reports. As a result, guidelines for therapy are based on very limited data, and often on few reported cases.

In this review, we analyze the available data regarding the impact of pregnancy on the course of cancer and the effects of the malignant process and its treatment on both the mother and her fetus. The purpose of this analysis is to identify areas where available data may allow clear conclusions as well as crystallization of questions which should have to be answered by future research.

Cancer in pregnancy

Cancer is the second most common cause of death during the reproductive years, complicating approximately 1/1000 pregnancies[1]. The most common malignancies associated with pregnancy include breast, cervix, leukemia, lymphoma, melanoma, thyroid, ovary, and colon. Because of the current trend for many women to delay child-bearing, the association of these malignancies with pregnancy is likely to increase. In previous decades, pregnancy was discouraged in patients with a history of cancer. However, in the current era such pregnancies are supported with more optimism. Conception in a patient over the age of 35, or in any patient believed to have diminished child-bearing potential, is considered a "valued pregnancy".

The discovery of cancer during pregnancy presents an extreme stress to both patient and physician. Because optimization of both maternal and

fetal outcomes may be impossible, compromise in the case of either mother or baby may be necessary. Clear guidelines for the management of these patients are essential, however, because the number of reported cases of pregnancy complicated by cancer is small and current management strategies are based on anecdotal reports, often presenting conflicting information[1].

One of the most common types of cancer during pregnancy is carcinoma of the breast. This cancer complicates 1/3000 pregnancies, representing 3% of all breast cancers[2]. Reports in the literature are limited to small numbers of patients, suggesting that stage for stage, the prognosis is the same for pregnant and nonpregnant patients. However, because pregnant patients often present with more advanced disease, they tend to have worse prognoses than nonpregnant patients of the same age[3]. While the outcome appears to be worse in patients below the age of 30 years[3] and in those diagnosed in the second half of pregnancy[4], the reasons for these tendencies are unknown.

The effect of the altered hormonal environment of pregnancy on the growth of breast tumors is the subject of controversy, with some authors reporting a more rapid progression of disease in pregnancy, while others report no such difference[3]. Several important questions remain unanswered. Is it ever safe to delay treatment because of the pregnancy? Is it safe to administer chemotherapy or radiation after the first trimester? Does the tumor progress more rapidly during pregnancy[2,3,5]? Should the pregnancy be terminated early? When and how should the baby be delivered?

Lymphomas are relatively common malignancies during the reproductive years. At the time of initial diagnosis or relapse of Hodgkin's disease, one-third of premenopausal patients are pregnant or have delivered within 2 years[6]. Sutcliffe and Chapman[7] suggested that "pregnancy does not affect the course of Hodgkin's disease and the disease does not affect the course of the pregnancy"; however, this conclusion was based on a review of the literature published prior to 1977. The treatment of the lymphomas depends on accurate staging, which requires such procedures as lymphangiogram, intravenous pyelography (IVP), computed tomography scans, and staging laparotomy[7–9] exposing the fetus to the potential risks of radiation and xenobiotics. As those patients with the earliest disease have the greatest chance of cure, it is crucial that accurate staging be performed. As in the case of breast cancer, a variety of questions remain unanswered: should therapy be delayed to optimize fetal outcome or instituted immediately to maximize the mother's chance of cure?

The acute leukemias are very rare during pregnancy, suggesting that

fertility may be diminished in these patients[10,11]. Although there is no evidence to date indicating that either the acute or chronic leukemias are altered by a coexisting pregnancy[12], the number of patients studied has been very small. Since acute leukemias are highly malignant but potentially curable, the best available regimen should be used in the woman presenting in the first trimester immediately following decision regarding the continuation of the pregnancy. Many reports exist of delivery of normal babies to women despite intensive treatment in subsequent trimesters[13,14].

Papillary adenocarcinoma of the thyroid, the most common of the thyroid neoplasms, has a peak age distribution in women of 30 to 34 years. The actual incidence of thyroid cancer during pregnancy is unknown. In patients under the age of 49, 90 to 95% survive 15 years[15,16]. Retrospective reviews suggest that pregnancy has a negligible effect on tumor progression[17,18]. However, treatment of this cancer is altered by the presence of a pregnancy: tumor ablation with radioactive iodine is contraindicated during pregnancy owing to adverse fetal effects, and, in patients with early disease, this therapy is offered postpartum.

In patients with more advanced disease, surgical excision of the tumor during pregnancy followed postpartum by radiotherapy is the treatment of choice[19]. In one study, radical neck dissection was followed by miscarriage in three of five patients[20].

Malignant melanoma is diagnosed in two to three of every 1000 pregnancies[21,22], and 30 to 35% of melanoma patients are women of reproductive age. Estrogen receptor protein has been isolated in melanoma cells, suggesting the possibility that this tumor may be hormone dependent[23]. However, the effect of pregnancy on the behavior of existing melanomas is in dispute because partial and complete postpartum regressions of melanomas have been reported[24–26]. Some authors report no effect of pregnancy on survival in patients with melanoma, whereas others report diminished survival in comparison with nonpregnant patients[27,28]. Here too, most reports are based on small numbers of patients.

Ovarian cancer is the fourth leading cause of all cancer deaths. However, it is so rarely diagnosed during pregnancy that solid management guidelines are lacking and it is unknown if pregnancy *per se* alters the natural history of the tumor. Experience in the nonpregnant state remains the basis for management[29].

Carcinoma of the cervix is the malignancy most commonly associated with pregnancy[30,31]. The Pap smear reveals abnormal cytology in 3% of pregnant patients with 4% of these due to invasive cancer. One out of every 30 cases of invasive cervical cancer occurs during pregnancy, complicating

1/1250 pregnancies. There is considerable controversy regarding the effect of pregnancy on the progression of cervical tumors. Findings from several studies suggest that the prognosis is poorer when there is an associated pregnancy, while others show no such detrimental effect[32,33]. Nisker and Shubert[33] reported an increased incidence of positive IB disease, as compared to nonpregnant patients. They also noted an increased risk of complications following radiation therapy and a lower 5-year survival rate in pregnant patients. Current unresolved issues include the following. Is there any benefit to delivery by cesarean section rather than vaginal delivery? What facts are needed for patients to consider termination of pregnancy? Should labor be induced? If so, at what gestational age should labor be induced? Should the pregnancy affect the decision to treat with surgery versus radiation?

Risks to the fetus

In discussing potential risk to the fetus associated with maternal cancer, one should consider the following:

1. The effect of chemotherapy and radiation on the developing fetus;
2. The effect of maternal anesthesia and surgery on the fetus;
3. The effect of maternal illness on fetal well-being.

Chemotherapy and radiation

With the establishment of sensitive analytical methods for measurement of drug levels in body fluids, it has become apparent that almost all xenobiotics are capable of crossing the placenta. Although cancer chemotherapy drugs belong to a variety of pharmacological groups, their common denominator is their ability to adversely affect cell division. Thus, the very qualities which make such compounds desirable for cancer therapy make them detrimental to the developing embryo. Animal studies reveal that almost all antineoplastic agents are teratogenic[34], and the sensitive period corresponds to the time of organogenesis (the first trimester in human pregnancy).

Evidence of teratogenic potential in humans is derived from case reports or small series. These total less than 250 cases as of 1987[34]. The American National Cancer Institute has established a registry of patients exposed to cancer chemotherapy during gestation. By 1987, 204 cases had been filed[35]. The generalizability of findings is highly tenuous because the denominator, or total number of such exposures, is not known. It can be argued, for

example, that clinicians choose to report only adverse outcomes, thus overrepresenting teratogenic potential of chemotherapy. Conversely, it may be argued that a normal outcome is deemed important enough to be reported[36].

Administration of chemotherapy in the first trimester of pregnancy exposes the embryo during embryogenesis to toxicity that may manifest an embryonic death or gross malformations[37]. Approximately 10% of fetuses exposed to cytotoxic drugs during the first trimester of pregnancy exhibit major malformations[38,39] compared to a rate of 1 to 3% in the general population. Among the cytotoxic agents, only aminopterin, a folic acid antagonist which is not used any more, has been shown to cause increased malformation rates[40]. There are at least 16 documented cases of teratogenic effect of the drug when used alone[34]. Methotrexate, a drug closely related to aminopterin was associated with birth defects in at least three cases but the rate of their occurrence is lower[34]. Their use should be avoided in the first trimester of pregnancy. Based on collection of case reports from the literature, the estimated relative risk for malformation was reported to be 1 : 9 for busulfan, 1 : 6 for cyclophosphamide, and 1 : 2 for chlorambucil[41]. Single reports exist on congenital malformation with the use of 5 flurouracil[40] and azothiomine[41] and arabinosyl cytosine[42,43]. Antibiotics (anthracyclines, bleomycin) and vinca alkaloids (vincristine, vinblastine) were not reported to cause malformation when administered during the first trimester[34].

There are only a few case reports regarding the use of single, other antineoplastics during early pregnancy. Although no association between the use of these drugs and congenital malformation was noted, their teratogenic risk cannot be estimated.

In a recent review of the literature, Doll *et al*[44] found that the rate of fetal malformation from combination of drugs in the first trimester is only slightly higher than observed with single agents; six (25%) of 24 cases versus 24 (17%) of 139 cases.

Based on small series and case reports, exposure to chemotherapy after the first trimester does not appear to pose an increased teratogenic risk. This observation is expected because embryogenesis of somatic organs is completed by 12 weeks. Brain development, by contrast, is a lengthier process. Consequently, xenobiotics are known to affect central nervous system development adversely in the second and third trimesters (e.g. methyl mercury, lead, and PCBs)[45–47].

Only one study is known to have measured long-term developmental outcome specifically. Aviles and Niz[48] examined 17 offspring of women with acute leukemia during pregnancy. Neurological, intellectual and

visual–motor–perceptual assessments were administered to the offspring who ranged in age from 4 to 22 years, and to siblings and unrelated controls. No differences were detected between the groups. Interpretation of the findings are constrained by the lack of presentation of data, the question as to whether the children were assessed "blind", and the use of a cross-sectional rather than a longitudinal design. Moreover, the inclusion in the sample of children whose mothers did not receive chemotherapy permits conclusions about the consequences of the disease, but it limits the understanding of the effects of chemotherapy. Notwithstanding the limitations, this study is important as the only existing examination of developmental outcome following exposure *in utero* to cytotoxic therapy. The general impression, based on case reports, is that chemotherapy does not have a major impact on later development. However, studies of the developmental teratogenicity of such environmental toxins as lead demonstrate that complex study designs are needed to detect small, but clinically relevant effects.

Other long-term adverse effects of *in utero* exposure to chemotherapy also must be considered. Recently in Toronto, a case of congenital malformation[49] was described in a child exposed *in utero* to cyclophosphamide for the treatment of maternal leukemia. The same child later developed both neuroblastoma and thyroid carcinoma. Of special interest is the fact that his twin sister is normal, suggesting the possibility of pharmacogenetic differences in metabolism of cyclophosphamide. Another example of the long-term teratogenic effects of *in utero* exposure to toxins is the occurrence of clear cell vaginal carcinoma in women exposed *in utero* to diethylstilbestrol[50].

Cancer chemotherapeutic agents are known to affect the fetal hematopoetic system. For example, cytopenia at birth has been described by a number of authors. However, because case reports yield little opportunity for statistical comparisons, the real risk of neonatal cytopenia following transplacental transfer of chemotherapeutic agents is unknown. Recently, Reynoso *et al*[49] surveyed existing case reports and integrated the findings with their own experience at the Toronto Leukemia Study Group. From this data base, they estimated that about one-third of all infants exposed *in utero* to chemotherapy will experience pancytopenia at birth[49].

Maternal exposure to radiation, either for diagnostic or therapeutic reasons, may increase fetal risks. To date, it is believed that fetal exposure to less than 0.05 Gy does not increase the teratogenic risk. In most diagnostic procedures, the cumulative exposure does not reach this dose level, even when the maternal abdomen is not shielded. However, the diagnosis of maternal cancer is often complicated and may require a

battery of radio-diagnostic tests whose cumulative radiation dose may potentially exceed the 0.1 Gy level. In the case of radiation therapy, substantially higher dose levels are involved, and these have been shown unequivocally to result in fetal damage, mainly to the brain, as evidenced by microcephaly and developmental delay[51].

Surgery

Surgery is conducted either to diagnose or to eradicate cancer. In both instances, the fetus is exposed to the potential risks from the transplacental effects of anesthetic agents, as well as to complications of maternal surgery. There are large published studies which establish the safety during pregnancy of the most commonly used anesthetic agents, including nitrous oxide, enflurane, barbiturates, and narcotics[34]. However, intraoperative complications, such as hypoxia, hypotension, hypovolemia, and decreased utero-placental perfusion secondary to prolonged maintenance in the supine position, as well as postoperative morbidity in the form of fever, infection, poor nutritional intake, or even pulmonary embolus, do threaten fetal well-being[44].

Maternal well-being

The cancer patient has an increased tendency to suffer febrile illness from infectious sources, drug fever, and/or the tumor *per se*. Numerous animal studies have shown a correlation between maternal hyperthermia and increased incidence of abortions and malformations, most notably microcephaly, microphthalmia, and skeletal defects[52–57]. Germain[58] found a threshold of 2.5 °C increase in core temperature for 1 hour was sufficient to induce malformations in rats, whereas increases in temperature of less than 2 °C were not found to be teratogenic. The sensitive period for teratogenesis was the era of gastrulation.

The relationship between hyperthermia and malformations in humans is less well defined. One obvious difficulty is the separation of the effects of fever from those of its cause, such as viral illness[59]. Many human studies do support the hypothesis that maternal febrile illness in early pregnancy is teratogenic, with neural tube defects and microphthalmia the most commonly noted anomalies. However, causal association has not been established[59–66].

Proper maternal nutrition is important for optimal neonatal and maternal outcome. However, the degree of maternal undernutrition which can be tolerated by the fetus without adverse effects has not been

established. Studies with animals have indicated that severe maternal undernutrition can result in stillbirths and increased perinatal mortality[67]. However, retrospective analysis of human data obtained during historical periods of starvation have revealed little or no adverse fetal effects[68].

Review of perinatal morbidity and mortality following severe food deprivation in the Netherlands during World War II revealed a mean decrease in birth weight of 8 oz, but no increase in congenital malformations or perinatal mortality[69]. Analysis of military screening examinations on all Dutch males at age 19 failed to disclose any difference in IQ score between boys whose mothers were starved during pregnancy and the general male population[70]. Elsewhere, studies have indicated adverse fetal effects following maternal malnutrition[71–74]. Additionally, studies have suggested that maternal ketoacidosis, as encountered in dehydration or severe weight loss, is potentially detrimental to fetal develpment[75,76].

Based on the above, it is evident that detriments in maternal well-being, such as malnutrition and fever, may pose additional risks to the developing embryo–fetus. These conditions are encountered more frequently in the cancer patient.

In summary, many questions regarding the management and outcome of the pregnant woman who develops a malignant disease and its impact on the fetus remain unanswered. The existence of pregnancy in the patient with cancer may have both a direct (e.g., hormonal changes) and indirect impacts on the course and management of the disease. This includes delay in diagnostic workup and treatment, choice of therapy, psychological stress, etc. In addition, chemotherapy and its associated side effects may bear teratogenic potential as well as long-term adverse effects such as developmental disturbances, infertility or malignancies.

The decision-making is complex due to physiological, moral, and ethical aspects of this extremely stressful situation. It is further complicated by the existence of only sparse data on both maternal and fetal outcome. Large, multicenter collaborative studies are needed to evaluate both the effects of pregnancy on the course of cancer and that of the malignant process and its treatment on the mother and her offspring. Such studies will allow the development of rational management policies.

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